can also be used on the biopsy tissue to detect viral infection.

Although the histologic patterns have been described individually, rejection, ischemia, and viral infections can occur simultaneously, with each contributing to a varying degree to the extent of liver injury.

RICHARD RAY, MD
KLAUS J. LEWIN, MD, FRCPath
Los Angeles

REFERENCES

Calne R (Ed): Liver Transplantation: The Cambridge-King's College Hospital Experience, 2nd Ed. Orlando, Fla, Grune & Stratton, 1987

Demetris AJ, Jaffe R, Starzl TE: A review of adult and pediatric post-transplant liver pathology. Pathol Annu 1987; 22 (pt 2):347-386

Ray RA, Lewin KJ, Colonna J, et al: The role of liver biopsy in evaluating acute allograft dysfunction following liver transplantation. Hum Pathol, in press

Snover DC, Freese DK, Sharp HL, et al: Liver allograft rejection: An analysis of the use of biopsy in determining outcome of rejection. Am J Surg Pathol 1987; 1:1-10

The Molecular Pathology of Prion Diseases

NEW PATHOGENETIC MECHANISMS are being discovered for the group of central nervous system (CNS) diseases that includes Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru in humans and scrapie in animals. These disorders have been grouped together because they have similar clinical, genetic, and histologic features—spongiform degeneration of neurons, astrocytic gliosis, and amyloid plaque formation—and because each is infectious. Originally it was postulated that they were caused by an atypical virus because of the small size of the infectious particle predicted from experimental studies and the absence of histopathologic features characteristic of viral infections. That possibility, however, is now considered unlikely because of studies at the University of California at San Francisco showing that highly purified preparations of the scrapie agent consist almost entirely of a single protein and no detectable nucleic acid. For this reason, the smallest infectious particle was termed a "prion" and the protein associated with infectivity was termed the "prion protein."

Although the structure of the prion and the precise role of the prion protein in infectivity are not known, it has been learned that the prion protein is an abnormal derivative of a normally expressed CNS nerve cell sialoglycolipoprotein. The normal isoform is synthesized continuously in hamster nerve cells, is highly susceptible to proteinase K digestion, and turns over rapidly. In contrast, the abnormal isoform resists proteinase K digestion, turns over slowly, and accumulates in the brain during scrapie. Moreover, the abnormal isoform of the prion protein accumulates precisely in those regions of the gray matter where spongiform degeneration of nerve cell processes and reactive astrocytic gliosis are greatest. It also polymerizes into the filaments that form the amyloid plaques characteristic of these diseases.

Evidence indicates that a human isoform of the scrapie prion protein causes Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru. Abnormal proteinase-resistant forms of the prion protein, which react specifically with anti-hamster prion protein antibodies, have been found in the brains of patients with Creutzfeldt-Jakob disease but not in normal brains or those of patients with Alzheimer's disease. The amyloid plaques in the brains of patients with Creutzfeldt-Jakob disease and those with the Gerstmann-Straussler syndrome react specifically with anti-hamster scrapie prion protein antibodies. Also, human chromosomes contain a single-copy prion protein gene that has been localized to chromosome 20. In addition, the amino acid sequence of the human prion protein is 90% homologous to the hamster and mouse prion protein. For these reasons, scrapie, Creutzfeldt-Jakob disease, the Gerstmann-Straussler syndrome, and kuru have been grouped under the term "prion disease."

The central pathogenic event in prion diseases appears to be the abnormal metabolism and accumulation of a normally expressed nerve cell protein. The unique feature of prion diseases is that the abnormal prion protein appears to participate in transmitting the disease. The prion hypothesis is consistent with the failure to find a virus and with the absence of an inflammatory or immune response. It is genetically consistent because although most cases of Creutzfeldt-Jakob disease are sporadic, 10% are dominantly inherited, and virtually all cases of the Gerstmann-Straussler syndrome are dominantly inherited. Furthermore, the scrapie incubation time gene is genetically linked to the prion protein gene in mice. Therefore, except for infectivity, most of the features of these diseases are difficult to reconcile with the viral hypothesis.

Prion research is now focused on determining the chemical differences between the normal and abnormal isoforms of the prion protein; whether the abnormal prion protein, either alone or with a cofactor, is the transmissible agent; and the molecular mechanisms by which prions induce disease.

STEPHEN J. DeARMOND, MD, PhD
San Francisco

REFERENCES

DeArmond SJ, Mobley WC, DeMott DL, et al: Changes in the localization of brain prion proteins during scrapie infection. Neurology 1987; 37:1271-1280

Prusiner SB: Prions and neurodegenerative diseases. N Engl J Med 1987; 317:1571-1581

Prusiner SB, DeArmond SJ: Prions causing nervous system degeneration. Lab Invest 1987; 56:349-363

Polymerase Chain Reaction—A Novel Method for Analyzing Specific DNA Sequences

THE ANALYSIS of DNA is becoming increasingly important in the study and diagnosis of hereditary, neoplastic, and infectious diseases. Often, however, the heterogeneity or small quantity of the sample available can limit the usefulness of conventional techniques. The polymerase chain reaction is a new enzymatic method for selectively replicating a specific nucleic acid sequence up to several hundred nucleotides in length within a complex mixture to facilitate its analysis.

To use the polymerase chain reaction procedure, the DNA sequences flanking the region of interest must be known. Two short oligonucleotide primers complementary to each of the two flanking regions but on opposite DNA strands are synthesized. These primers are added in vast molar excess to the sample DNA, which is then denatured and allowed to anneal to the primers. In the presence of deoxyribonucleoside triphosphates, a thermostable form of bacterial DNA polymerase uses each oligonucleotide as a primer to synthesize a copy of the adjacent DNA strand; each newly synthesized strand then provides a new template for synthesis from the opposite primer. By repeated cycles of denaturation, annealing, and synthesis, the region between the two primers is amplified exponentially. A 220,000-fold amplification of the desired region can be achieved after 20 such cycles; the amplified sequence can then be analyzed by a variety of techniques. Automated instrumentation capable of pro-